Remarks

We note with appreciation the establishment of the requested CPA and withdrawal of some of the rejections previously applied.

The Specification has been amended to recite the citations of the four references listed at page 11, lines 17-22 without adding new matter.

Claims 1, 2, 4-8, 10, 12, and 15-17 are present in the case, Claims 3, 9, 11, 13, and 14 being hereby withdrawn. No new matter has been added.

Claim 7 has been amended to independent form.

Turning to the rejection of Claims 1, 2, 4-6, 10, 12, and 15-17 under 35 U.S.C. §112, first paragraph, we respectfully submit that the amendments to the claims place them in proper form for allowance. Specifically, Claim 10 as amended is no longer directed to all possible reverse transcriptases. Rather, Claim 10 has been amended to recite a reverse transcriptase comprising an amino acid sequence of Tyr-Xaa_6-Asp-Asp (SEQ ID NO.50), wherein $Xaa_6$is alanine or cysteine. According to the revised guidelines concerning compliance with the written description requirement of 35 U.S.C. §112, first paragraph, "all disclosed distinguishing identifying characteristics" are to be considered, including partial structure, physical and/or chemical properties, functional characteristics, known or disclosed correlation between structure and function, method of making, and combinations thereof. All of the identified factors are to be weighed in view of the level of skill and knowledge in the art and in light of and consistent with the written description. If on that basis it is determined that one of ordinary skill in the art would recognize from the disclosure that the

applicant was in possession of the claimed invention, the written description requirement is satisfied.

In this case, the claims recite both structure and function. Specifically, the claimed reverse transcriptases must have a YXDD box and must either be capable of synthesizing msDNA or must have reverse transcriptase activity. Additionally, we agree with the Examiner that at least seven working examples of the claimed invention have been provided. Thus, in light of the Specification, one of ordinary skill in the art would recognize that the applicant was in possession of the claimed invention. Therefore, we respectfully submit that Claims 1, 2, 4-6, 10, 12, and 15-17 satisfy 35 U.S.C. §112, first paragraph.

Moreover, we respectfully submit that the order of the amino acid sequences set forth in Claim 12 is fully supported by Figure 14. The description of Figure 14 states that the amino acid sequences of the bacterial RTs are numbered from the amino terminal end of the sequence. As such, Figure 14 clearly demonstrates the claimed order of sequences. For example, the second line of Sa163 in Figure 14 starting with residue 225 contains the amino acid sequence SVTW, the third line beginning with amino acid 293 contains the amino acid sequences NAL and YADD, and the fourth line beginning with residue 360 contains the amino acid sequence RVTG. Thus, we respectfully submit that Claim 12 as amended fully satisfies the requirements of 35 U.S.C. §112.

Turning to the application on its merits we respectfully submit that the Lim and Mass reference fails to anticipate Claims 1, 2, 5, 6, 8, 10, and 15-16 as amended. Independent Claims 1, 10, and 15 require the presence of the amino acid sequences Tyr-Xaa_6-Asp-Asp and Asn-Xaa_1-Xaa_2 wherein Xaa_1 is a hydrophobic residue selected from the group

consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine. In sharp contrast, the Lim and Mass article fails to teach or suggest the presence of an amino acid sequence comprising Asn-Xaa_1-Xaa_2. Therefore, we respectfully submit that the Lim and Mass article cannot anticipate amended Claims 1, 2, 5, 6, 8, 10, and 15-16.

Applicants' submit herewith a Declaration under 37 C.F.R. §1.131 to swear behind the publication by Rice et al. Applicants maintain that Rice et al. is not prior art because the invention, as embodied in the claims, had been reduced to practice prior to the publication of Rice et al. in July 1993. Applicants attach hereto a properly executed declaration pursuant to 37 C.F.R. §1.131 to that effect. The Declaration has been executed by all but one inventor, Mr. Jorge Vallejo-Ramirez, who could not be found. A Declaration under 37 C.F.R. § 1.47 requesting acceptance despite the missing signature is also enclosed. By this submission, Applicants respectfully that the §103 rejections in view of Rice et al. be withdrawn. The Office Action indicates that the 37 C.F.R. § 1.131 Declaration should predate the filing date of one of the cited patents. However, since the Rice publication is relied upon in maintaining the rejection, antedating the Rice publication defeats the obviousness rejection, since the disclosure of Rice is no longer available. Antedating a single reference in a combination of references is sufficient to overcome the rejection. Accordingly, the rejections based on hypothetical combination with Rice should be withdrawn.

Furthermore, we respectfully submit that neither of the Inouye patents, Hsu, or Xiong teaches or suggests the necessity of the conserved Asn-Xaa_1-Xaa_2 sequence. We

accordingly respectfully submit that any hypothetical combination of either of the Inouye patents with Hsu and Xiong cannot preclude patentability of the solicited claims.

Turning to a hypothetical combination of Hsu with Lim and Mass, we respectfully submit that no motivation to combine the two references exists. Specifically, Hsu discloses the similarity of RTs in *M. xanthus* and *S. aurantiaca* but teaches away from a combination with a reference related to an *E. coli* RT on pages 2385-2387 by stating that only 13% of *E. coli* natural isolates contain retrons, and those retrons show substantial diversity. Since the teaching of Lim and Mass relates to such an *E. coli* RT, no motivation to combine the cited references has been established on this record.

We further respectfully submit that any hypothetical combination of Hsu and Lim and Mass does not render Claims 1, 2, 4-6, 8, 10 and 15-16 as amended obvious. As previously noted, Lim and Mass fails to teach or suggest the presence of the claimed amino acid sequence Asn-Xaa_1-Xaa_2. Similarly, Hsu fails to teach or suggest the necessity of the conserved Asn-Xaa_1-Xaa_2 sequence. We accordingly respectfully submit that the rejection based on Hsu in view of Lim and Mass be accordingly withdrawn.

In light of the foregoing, we respectfully submit that the solicited claims are in proper form for allowance. Early notification to that effect is respectfully requested.

Respectfully submitted,

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Marked-Up Version Showing Changes Made to the Specification

Please replace the first paragraph on page 11 with the following:

Figure 14 shows the amino acid sequence alignment of bacterial RT carried out according to Xiong and Eickbush EMBO Journal, 9(10): 3353-3362, (1990). Amino acids highly conserved in eukaryotic Rts are shown at the top of the sequences. These amino acids include largely unvaried residues or chemically similar residues. (h) Hydorphobic residue; (p) small polar residues; (c) charged residue. Amino acids conserved in all seven bacterial Rts (identical residures plus functional conserved residues indicated by h for hydrophobic residues or p for polar residues) are marked by solid dots at the bottom of the sequences. The consensus sequence shown at the bottom of the sequences is determined when five out of seven sequences contain an identical or chemically similar residue (h, hydrophobic residue; p, charged and polar residue). The subdomains 1 to 7 are according to Xiong and Eickbush (1990), which are boxed and indicated by numbers. The highly conserved YXDD sequences are also boxed. Numbers on the right indicate the amino acid positions from the amino terminus for each RT Sources for the sequences are Sal63 (Hsu et al. J. Bact., 174(7): 2384-2387, April 1992b) Seq. ID No. 34, Mx162 (Inouye et al. 1989) Seq. ID No. 33, Mx65 (Inouye et al. 1990) Seq. ID No. 32, Ec67 (Lampson et al. 1989b) Seq. ID No. 35, Ec86 (Lim and Maas 1989) Seq. ID No. 36, Ec73 (Sun et al. 1991) Seq. ID No. 37, and Ec107 (Herzer et al. 1992) Seq. ID No. 38.

Marked-Up Version Showing Changes Made to the Claims

1. (Three Times Amended) ~~The~~An isolated and purified bacterial reverse transcriptase (RT) ~~of claim 13,~~which synthesizes msDNA, which is essential for the synthesis of msDNA *in vivo*, and which RT ~~contains~~comprises a sequence of amino acid residues as follows: Tyr-Xaa$_6$-Asp-Asp (SEQ ID No:50), wherein Xaa$_6$ is alanine or cysteine~~, as shown in SEQ ID No.50~~ and further comprising a sequence of amino acid residues as follows: Asn-Xaa$_1$-Xaa$_2$, wherein Xaa$_1$ is a hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa$_2$ is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine.

2. (Three Times Amended) The bacterial RT of claim 1 which contains a second sequence of amino acid residues as follows: ~~Ser-Xaa-Xaa$_1$-Xaa$_2$~~Ser-Xaa$_3$-Xaa$_4$-Xaa$_5$, wherein Xaa$_3$ is a hydrophobic residue selected from the group consisting of valine, phenylalanine, leucine, and isoleucine, Xaa$_{1-4}$ is a polar residue selected from the group consisting of threonine, asparagine, lysine, and serine, and Xaa$_{2-5}$ is a hydrophobic residue selected from the group consisting of tryptophan, phenylalanine, and alanine, as shown in SEQ ID No:51.

4. (Three Times Amended) The bacterial RT of claim ~~3~~2 which contains a fourth sequence of amino acid residues as follows: Xaa$_7$-Val-Thr-Gly, wherein Xaa$_7$ is a polar residue selected from the group consisting of arginine, glutamic acid, lysine, valine, and glutamine, as shown in SEQ ID No:45.

7. (Three Times Amended) ~~The bacterial RT of claim 6 which contains~~An isolated and purified bacterial reverse transcriptase (RT) which synthesizes msDNA and which is essential for the synthesis of msDNA *in vivo*, said RT comprising a sequence of amino acid residues as follows: Tyr-Xaa_6-Asp-Asp, wherein Xaa_6 is alanine or cysteine, as shown in SEQ ID No:50, wherein said sequence is located in subdomain 5 shown in Fig. 14 at positions 175-191 of SEQ ID No:32, at positions 175-191 of SEQ ID No:33, at positions 175-191 of SEQ ID No: 34, at positions 168-184 of SEQ ID No: 35, at positions 159-175 of SEQ ID No:36, at positions 171-187 of SEQ ID No:37, and at positions 157-173 of SEQ ID No:38, and further comprising the 61 amino acid residues as shown by black dots in Figure 14 of SEQ ID NOs:32-28, wherein h is a hydrophobic residue and p is a small polar residue.

10. (Amended) ~~The bacterial RT of claim 9,~~A reverse transcriptase extension *in vitro* screening test method for determining the presence or absence of msDNA in a bacterium comprising:

treating a preparation of total RNA extracted from said bacterium with a reverse transcriptase in the presence of a radiolabeled deoxynucleotide, wherein said RT, when msDNA is present in the total RNA of the bacterium, utilizes the DNA portion of the msDNA as a primer and the RNA portion of the msDNA as a template for radiolabeling the DNA portion of the msDNA, and wherein said RT comprises a sequence of amino acid residues as follows: Tyr-Xaa_6-Asp-Asp (SEQ ID No:50) where Xaa_6 is alanine or cysteine, and a sequence of amino acid residues as follows: Asn-Xaa_1-Xaa2, wherein Xaa_1 is a

hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine

electrophoresing the treated RNA preparation, and

determining the presence of msDNA in the bacterium by detecting a band of radiolabeled DNA, said band being indicative of the presence of msDNA in the bacterium,

wherein said bacterium is selected from the group of genera consisting of Myxococcus, ~~Escherichia,~~ Proteus, Klebsiella, Flexabacter, Cytophaga, Stigmatella, Salmonella, Nannocystis, Rhizobium, and Bradyrhizobium.

12. (Three Times Amended) The isolated and purified RT of claim 4 ~~in which the amino acid sequences Ser-Xaa-Xaa$_1$, Try-Xaa-Asp-Asp (SEQ ID No:50), and Xaa-Val-Thr-Gly (SEQ ID No:52) are arranged in order starting from the amino terminal end of the RT~~ which RT has in the following order starting from the N- to the C-terminus:

(1) an amino acid sequence of Ser-Xaa_3-Xaa_4-Xaa_5 (SEQ ID No: 51), wherein Xaa_3 is a hydrophobic residue selected from the group consisting of valine, phenylalanine, leucine, and isoleucine, Xaa_4 is a polar residue selected from the group consisting of threonine, asparagine, lysine, and serine, and Xaa_5 is a hydrophobic residue selected from the group consisting of tryptophan, phenylalanine, and alanine;

(2) an amino acid sequence of Asn-Xaa_1-Xaa_2, where Xaa_1 is a hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine;

(3) an amino acid sequence Tyr-Xaa_6-Asp-Asp (SEQ ID No: 50) wherein Xaa_6 is alanine or cysteine; and

(4) an amino acid sequence Xaa_7 is a polar residue selected from the group consisting of arginine, lysine, glutamic acid, glutamine, and valine.

15. (Amended) ~~The~~An isolated and purified reverse transcriptase ~~of claim 14~~which is a prokaryotic reverse transcriptase, which comprises a YXDD (tryosine-X·aspartic acid-aspartic acid) box and an amino acid sequence Asn-Xaa_1-Xaa_2, wherein Xaa_1 is a hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine.

17. (Three Times Amended) The isolated and purified bacterial reverse transcriptase (RT) of claim ~~13~~1 which RT has in the following order starting from N- to the C- terminus, an amino acid sequence of Asn-Xaa_1-Xaa_2, where Xaa_1 is a hydrophobic residue selected from the group consisting of alanine, leucine and phenylalanine and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine and isoleucine, an amino acid sequence of Ser-Xaa_3-Xaa_4-Xaa_5 (SEQ ID: 51), wherein Xaa_3 is a hydrophobic residue selected from the group consisting of valine, phenylalanine, leucine and isoleucine, Xaa_4 is a polar residue selected from the group consisting of threonine, ~~asparagines~~asparagine, lysine and serine, and Xaa_5 is a hydrophobic residue selected from the group consisting of tryptophan, phenylalanine and alanine, an amino acid sequence of

Tyr-~~Xaa$_5$~~Xaa$_6$-Asp-Asp (SEQ ID No: 50), where ~~Xaa$_5$~~Xaa$_6$ is alanine or cysteine, an amino acid sequence of ~~Xaa$_6$~~Xaa$_7$-Val-Thr-Gly (SEQ ID No: 52), where ~~Xaa$_6$~~Xaa$_7$ is a polar residue selected ~~form~~from the group consisting of arginine, lysine, glutamic acid, glutamine and valine.

Please cancel Claims 3, 9, 11, 13 and 14 without prejudice and without disclaimer of the subject matter contained therein.